EXHIBIT 3

2560.0020000

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,244	09/21/2001	Tony W. Ho	2560.0020000	4326

26111 7590 03/16/2009

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

TW
DOS

EXAMINER	
LANKFORD JR, LEON B	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
03/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/960,244	HO ET AL.	
	Examiner	Art Unit	
	Leon B. Lankford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,21,25,26 and 97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,21,25,26 and 97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/5/2008, 11/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's arguments, declarations and amendments filed 3/5/08 & 7/7/08 have been fully considered.

The prior art as applies to MAPC has been overcome by applicant's amendments and arguments. The examiner maintains the position that the claimed cell population is not distinct from a population of Mesenchymal Stem Cells (MSCs).

Applicant has argued that the claimed cell population is not a population of Mesenchymal Stem Cells (MSC) because they express different cell surface markers. This argument has been fully considered and has been oft –debated between applicant's representatives and the examiner. It is unclear that the presence of one or even a few differences in cell surface markers is indicative of a new cell type. This is particularly true wherein there is no apparent functional change in the cell. Furthermore, it is apparent from the literature on the subject that not all cell surface markers are conserved. i.e. are always present or absent from a particular cell type. As such, the claimed cells would appear to be functionally the same as what the prior art calls mesenchymal stem cells differing only in the presence or absence of a few cell surface markers that have not be shown to have any bearing on the fundamental functions or characteristics of the cells. To support his argument, the examiner has cited three review articles (Baksh, Lodie & Chamberlain) which all show that MSCs have some small phenotypic differences depending on their culture conditions.

Applicant has attempted to differentiate the claimed population from MSCs by indicating that the method for preparing the population differ from the methods of

preparing/isolating MSCs. An analysis of applicant's specification does not seem to yield a description of a method which would yield cells other than MSCs.

Applicant argues that the claimed cells are isolated from a low density gradient fraction and that the claimed cells are isolated from a high density gradient fraction. However as indicated in the declaration of applicant, the media and methods for isolation are not the same and as such it is unclear how that cells can be established as different based on the density gradient fraction from which they are isolated. It should be noted as well that the claims are not limited to a functional definition of which fraction the cells are isolated from. New claim 97 would be suggestive that the density gradient fraction is not critical. Applicant's arguments and the claims would appear to be in conflict.

Further, applicant would appear to argue that the production of the cells under "low oxygen" is key in the production of the instant cell population however applicant's function definition (see applicant's examples) of low oxygen would seem to encompass a range from 5% oxygen to about 23% oxygen (an concentration greater than the concentration of oxygen in air) as applicant's function definition encompasses a 90% air/ 5% oxygen composition.

It is unclear from applicant's specification what is critical to the production of a cell population which is different from MSCs. Applicant's specification (cited by applicant for support of new claim 97) does not demonstrate a method which has critical steps which would yield a population other than MSCs:

> Human bone marrow cells are obtained from healthy human donors byaspirations of the iliac crest and bone marrow stromal cell populations obtained employing well established techniques. For example, substantially homogenous cell populations which co-express CD49c and CDg0 are obtained from human iliac crest bone marrow aspirates and processed to mononuclear cell fractions from which bone marrow stromal cells are selectively propagated *in vitro* based upon their propensity to attach to plastic and divide in response to defined cell culture medium. The plastic-adherent cells are optimally grown at a cell concentration that encourages virtually only the self-renewing cells, referred to as colony-forming unit fibroblast-like cells (Cfu-f), to proliferate. The Cfu-f-derived cells are analyzed for cells which co-express CD49c and CD90 and sub-cultured to produce a substantially homogenous cell population which co-express CD49c and CD90.

Applicant s have argued (particularly in the previous interview) that the claimed cell population is different from MSCs and that in fact there are substanative and lasting phenotypic differences in the cells as compared to MSCs. This argument has not been substantiated in the response of 7/2008 and in fact it is unclear what method actually produces the cell population which is applicant's invention. As such the product-by-process claim is rejected over the same art.

Claim Rejections - 35 USC § 112

The previous rejection under the first paragraph of 35 U.S.C. 112 has been overcome by applicant's amendments and arguments,

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 97 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claim 97 is rejected for containing new matter. The examples cited for support do not contain the limitation of a seeding density of "less than about 2500 cells/cm^{2}" and in fact Example 1 differs greatly from the claimed invention despite the fact that the method in Example 1 is alleged to be the method which produces the claimed cell population.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 97 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 97 is rendered indefinite by the limitation "low oxygen" because it is unclear what the intended metes and bounds of a "low oxygen" condition are.

Applicant's function definition (see applicant's examples) of low oxygen would seem to encompass a range from 5% oxygen to about 23% oxygen (an concentration greater than the concentration of oxygen in air) as applicant's function definition encompasses a 90% air/ 5% oxygen composition and as such would not appear to define a "low oxygen" concentration at all.

Specification

The amendment filed 7/7/8 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: applicant has amended the specification to move the description of the cells produced from Example 1 to Example 3 and this would appear to be new matter and not simply a correction of a clerical error. Methods 1 & 3 are distinct methods and it would appear by making the instant amendment, applicant is changing the description of the invention.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14, 21, 25-26 & 97 are rejected under 35 U.S.C. 102(b) as being anticipated by Haynesworth et al. (1998, U.S. Patent 5,733,542) taken in light of Pittenger et al. (1999, *Science* 284: 143-147), Woodbury et al. (2000, *Journal of Neuroscience Research* 61: 364-370), and Lee et al. (2000, *Hepatology* 40: 1275-1284).

Haynesworth et al. teach a population of mesenchymal stem cells (MSCs) isolated from human adult bone marrow (Example 1; column 3, line 18, through column 4, line 51).

Pittenger et al. is cited as evidence that the MSCs of Haynesworth et al. can differentiate to various mesodermal cell lineages, including bone, cartilage, and adipose (Figure 2).

Woodbury et al. is cited as evidence that the MSCs of Haynesworth et al. can differentiate to neurons, (page 364, column 1, paragraph 1; page 365, column 2, paragraph 2, through page 367, column 2, paragraph 3).

Lee et al. is cited as evidence that the MSCs of Haynesworth et al. can differentiate to hepatocytes, (page 1277, column 1, paragraph 3; page 1279, column 1, paragraphs 2 and 3; Figure 2).

To invalidate a patent by anticipation, a prior art reference normally needs to disclose each and every limitation of the claim. See *Standard Havens Prods., Inc. v.*

Gencor Indus., Inc., 953 F.2d 1360, 1369, 21 USPQ2d 1321, 1328 (Fed. Cir. 1991). However, a prior art reference may anticipate when the claim limitation or limitations not expressly found in that reference are nonetheless inherent in it. See *id.* and *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 630, 2 USPQ2d 1051,1053 (Fed. Cir. 1987). Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. See *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). **Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art.** See *Titanium Metals*, 778 F.2d at 780. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. See *id.* at 782. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. See *id.* at 782 ("Congress has not seen fit to permit the patenting of an old [composition], known to others..., by one who has discovered its...useful properties."); *Verdegaal Bros.*, 814 F.2d at 633.

This court's decision in *Titanium Metals* illustrates these principles. See *Titanium Metals*, 778 F.2d at 775. In *Titanium Metals*, the patent applicants sought a patent for a titanium alloy containing various ranges of nickel, molybdenum, iron, and titanium. The claims also required that the alloy be "characterized by good corrosion resistance in hot brine environments." *Titanium Metals*, 778 F.2d at 776. A prior art reference disclosed a titanium alloy falling within the claimed ranges, but did not disclose any corrosion-resistant properties. This court affirmed a decision of the PTO Board of Appeals finding

the claimed invention unpatentable as anticipated. This court concluded that the claimed alloy was not novel, noting, "it is immaterial, on the issue of their novelty, what inherent properties the alloys have or whether these applicants discovered certain inherent properties." *Id.* at 782. This same reasoning holds true when it is not a property, but an ingredient, which is inherently contained in the prior art. The public remains free to make, use, or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle." See *Atlas Powder Co. v. IRECO Inc.*, 51 USPQ2d 1943 (Fed. Cir. 1999).

Thus, a reference may be anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. A reference includes an inherent characteristic if that characteristic is the natural result flowing from the reference's explicitly explicated limitations. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

While the prior art does not clearly disclose all of applicant's claimed limitations, it would appear that the cells claimed are a population of MSCs as disclosed by Haynesworth. M.P.E.P. § 2112 reads, "The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." Something that is old does not become patentable upon the discovery of a new property, use, or application. Even if applicants had identified properties of the MSCs of Haynesworth et al. that Haynesworth et al. did not or could

not test for, in this case the cells' telomerase expression level and ability to differentiate to various cell lineage types, such an identification would not render the MSCs of Haynesworth et al. patentable.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not Applicants' cells differ and, if so, to what extent, from that discussed in the references including the ability of the cell population to maintain its doubling rate. Therefore, with the showing of the references, the burden of establishing non obvious by objective evidence is shifted to Applicants. Significantly, applicant provides no factual evidence whatsoever to refute the holding of anticipation or obviousness. Note specifically that on the current record the only way of overcoming such a clear holding of anticipation is factual proof that the rejection is in error. *See* MPEP § 2112, disclosing that once a proper holding of anticipation is made, the burden shifts to applicant to demonstrate an unobvious difference between the claims and the prior art. *See also*, *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) ("the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product").

[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on `inherency' under 35 U.S.C. 102, on `prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to

product - by - process claims. Quoting *In re Fitzgerald,* 619 F. 2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (itself quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 - 34 (CCPA 1977)).

Note that MPEP § 706.3(e) states that:

> "[w]hen the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 35 U.S.C. 102 or 35 U.S.C. 103 of the statute is appropriate. As a practical matter, the Patent and Trademark Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith. A lesser burden of proof is required to make out a case of prima facie obviousness for product-by-process claims because of their peculiar nature than when a product is claimed in the conventional fashion. *In re Brown*, 59 CCPA 1063, 173 USPQ 685 (1972) ; *In re Fessmann*, 180 USPQ 324 (CCPA1974)."

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply

with 37 CFR 3.73(b).

Claims 14, 21 & 25-26 & 97 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14, 19-21 and 24-25 of copending Application No. 10/251685. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to the same cell population wherein applicant has simply specified an inherent limitation in the instant case which is not claimed in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant argues (in '685) that the claimed cell population is distinct and unobvious over the population claimed in that application because of the limitation "induced to express" cardiac factors however this argument is not found persuasive. A transient phenotypic change, e.g. the induction of a transcription factor, does not preclude a holding of anticipation because it does not result in a material difference between the cells in question. A living cell's phenotype can change with something as simple as feeding the cell with a carbon source or providing an enzymatic cofactor but that does not change the identity of the cell *per se*. If a phenotypic change is merely the result of a culture method and not an actual change in the differentiation state or genotypic state of a cell then the cell per se has not become a new cell and it thus not novel over the cell before the culturing change. The examiner will illustrate his point with two disparate examples:

It is clear that if one induces a hematopoeitic stem cell (HSC) to differentiate into an erythrocyte, the HSC and erythrocytes are distinct cells. The erythrocyte is genotypically and functionally different from the HSC and the change is not transient and not reversible.

It is also clear that if an embryonic stem cell (ES) is exposed to LIF, it will not spontaneous differentiate into another cell variety of endothelial or epithelial origin but one would not consider the ES in solution with the LIF to be a different and distinct cell from the ES in a culture medium that doesn't contain LIF.

It is the examiner's contention that the instant scenario (the induction of transcription factors) is more akin to the second example (ES cells & LIF) and thus the cells *per se* would not be considered unobvious or even novel over the cells disclosed in the '244 application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leon B. Lankford whose telephone number is 571-272-0917. The examiner can normally be reached on Mon-Fri 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651